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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,614	11/15/2001	David Botstein	P2730P1C29	7398

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,614	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126, 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7//5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's Brief and amendments, filed on 28 October 2005 and 5 July 2006, have been entered.

Claims 1-118, 127 and 128 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 119-126 and 129-131 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

Continuity

The objection to the Application for not complying with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), is *withdrawn*. The provisional application contains references to the PRO1097 polypeptide. Therefore, the filing date of 16 June 1997 is considered as the priority date.

Maintained/New Objects and Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. The basis for this rejection is set forth at pp. 4-8 of the previous Office Action (20 October 2004).

Claims 119-126 and 129-131 are directed to the polypeptide of SEQ ID NO: 349. The claims also recite a polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide of SEQ ID NO: 349, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044; wherein the nucleic acid encoding the polypeptide is over-expressed in lung or colon tumor cells. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

Applicant's arguments in the response submitted 5 July 2006, as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons:

At p. 2 of the 5 July 2006 Response, Applicants assert that it was well known in the art at the time the invention was made that gene amplification imparts a credible, substantial and specific utility for PRO1097 polypeptides. They go on to state that Example 170 of the

specification discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9B. Applicants explain that a ΔCt value of at least 1.0 was observed for PRO1097 in at least three of the tumors listed in Table 9B. Applicants argue that PRO1097 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or approximately 2.3 fold in two lung tumors and 3 colon tumors. Applicants submit that the Specification has not only disclosed that the DNA copy number for the gene encoding PRO1097 is increased in several different tumors, but has also quantified the degree of gene amplification observed in each of these tumors. At p. 4-5 of the 5 July 2006 Response, Applicants cite the Declaration of Dr. Polakis and contend that absence any evidence to the contrary, the 2.3-fold amplification disclosed for the PRO1097 gene is significant. They also state that a positive result from some tumors, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon). However, there is no evidence regarding whether or not PRO1097 mRNA or polypeptide levels are also increased in these cancers. Further research needs to be done to determine whether the small increase in PRO1097 DNA supports a role for the peptides in the cancerous tissue; such a role has not been suggested by the instant disclosure. It is not known whether PRO1097 is expressed in corresponding normal tissues, and what the relative levels of expression are. For example, the gene amplification data presented in the specification were problematic. The control DNA appeared

to be from blood rather than from a matched tissue sample (i.e., healthy lung and colon), while the literature shows that matched tissue samples are the standard (Pennica et al.; cited in the Office Action of 20 October 2004). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen; cited previously). Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1097 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid correlates with an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (see *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689)).

In reference to the Declaration under 37 C.F.R. §1.132, by Dr. Polakis, the examiner maintains that the Declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed polypeptides, which are produced by the nucleic acid which is alleged to be significantly amplified in cancer. Applicants discuss the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number and that this increase is significant and useful. Applicants direct the examiner to page 3 of the Polakis Declaration that describes the gene amplification technique in the present application, and references that attest to the use of this technique in diagnostic and prognostic fashion.

This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1097 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1097 nucleic acid was amplified in two types of cancer samples (lung and colon), to a minor degree (about 2.11 to 2.53 fold). No mutation or translocation of PRO1097 has been associated with any type of cancer versus normal tissue.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis's conclusions are provided in the declaration. Therefore, the Polakis declaration is not persuasive as it relates only to the issue of nucleic acid and not to the claimed subject matter, which is polypeptides, and furthermore, *if* the claims were directed to nucleic acids, would still have not been persuasive.

Applicants state that based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1097 gene is amplified, the PRO1097 polypeptide would be more likely than not overexpressed (p. 3, Response). Applicants conclude that based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed PRO1097 polypeptide.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification does not disclose that the PRO1097 polypeptide levels increase or stay the same, or even that the protein is expressed at all. Further research would be needed to reasonably confirm whether or not there is a change in PRO1097 polypeptide levels in cancers that show

amplification of the PRO1097 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO1097 polypeptides as claimed in this application are simply starting points for further research and investigation into the potential practical uses of the polypeptides. There is no "overwhelming" evidence from the gene amplification data in the specification indicating that the gene encoding PRO1097 is significantly amplified in certain lung and colon tumors. The art such as Hu et al., (submitted with the Office Action of 20 October 2004) evinces that at the *observed* levels of gene amplification, there is *not* a probable correlation between gene copy number and protein levels. The art, again as evidenced by Hu et al., considers the standard in asserting such a correlation to require actually examining the protein levels, which Applicant has not done. Therefore, neither the specification as filed nor the general knowledge in the art support the asserted utility as being substantial, i.e. as being anything but an invitation to further experimentation.

Contrary to Applicants' assertions (p. 4, Response), there is no evidence regarding whether or not PRO1097 mRNA or polypeptide levels are increased in these cancers. Furthermore, what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica et al.). Pennica et al. and Sen et al. (submitted 20 October 2004) establish that gene amplification is a general feature of cancer, and that it is not predictable that the amount of amplification seen for PRO1097 is predictive of protein levels, and hence that the claimed polypeptides lack a readily available utility. While Pennica et al. is directed to small numbers of genes, the instant application only concerns each gene and the respective protein it encodes. Applicants have not provided any testing of the role, activity, or expression of the PRO1097 polypeptide in cancer. Thus, there is no basic principle of correlation as urged by

Applicant; rather, the art as a whole teaches toward a *lack of expectation* of a correlation for a gene that is amplified, consistent with the data proffered for PRO1097.

Furthermore, as discussed by Haynes et al (cited in the Office Action of 20 October 2004), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. As discussed above, Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. (cited in the Office Action of 20 October 2004) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found ($r = -0.025$), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung

adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

In the Response of 5 July 2006, Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis. Applicants also cite numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicants assert that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicants also contend that the references and the Polakis Declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of p. 453).

Furthermore, all of Applicant's newly cited references (with the exception of Orntoft et al.) measure mRNA, not just gene amplification, which is the assay utilized in the instant Specification. Also, with the exception of Futcher et al., all of Applicant's newly cited

references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicants that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner).

With regard to the Ornoft reference, Applicants submit at p. 5 of the 5 July 2006 Response that Ornoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Ornoft have been fully considered but are not found to be persuasive. Ornoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed "CGH," and was quite different than the method used in the instant Specification. Ornoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at one time. In fact that group concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1097 in the instant specification. That is, it is not clear whether or not PRO1097 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Ornoft et al. is not clear.

Applicants also assert that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and reported a good correlation between protein abundance, mRNA

abundance, and codon bias. Applicant's arguments have been fully considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (p. 7368, col 1). Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (p. 7367, col 1, 1st full paragraph).

The Examiner maintains the previous argument of record, namely that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments at p. 3-4 of the 5 July 2006 Response, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated.

The specification of the instant application has only disclosed that the PRO1097 polynucleotide is overexpressed in lung and colon tumors. The specification does not indicate that the PRO1097 polypeptide has been overexpressed in the lung and colon tumor samples tested. Given the asserted increase in PRO1097 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO1097 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of

the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and, "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO1097 polypeptides have utility in the fields of cancer diagnostics is not substantial.

Along with the Polakis Declaration, submitted 5 July 2006, Applicants have submitted a Table that scores tumor mRNA versus tumor immunohistochemistry. Applicants argue that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 5 July 2006 has been considered and is deemed insufficient to overcome the rejection of claims 119-126 and 129-131 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, data for PRO1097 does not seem to appear in the table (Exhibit B). It is not clear which "UNQ" number refers specifically to PRO1097, if any at all. Furthermore, it is not clear how the clones appearing in the table compare to PRO1097, or if the results presented in the table were determined by the same methodology as presented in Example 170 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? In addition

mRNA was used in microarrays, not amplified genomic DNA as in the instant application. And the control appeared to be normal tissue, not pooled blood as in the instant Application.

The specification fails to precisely disclose any correlation between the reported overexpression of PRO1097 mRNA and PRO1097 protein expression, and more importantly, to what extent PRO1097 mRNA is reliably overexpressed in a particular tumor sample, such as lung and colon, such that the PRO1097 polypeptide encoded thereby could be used as a diagnostic marker for lung and colon tumors. There is no evidence regarding whether or not PRO1097 polypeptide levels are overexpressed in lung and colon tumors.

Further research needs to be done to determine whether the small increase in PRO1097 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. It is not known whether PRO1097 is expressed in corresponding normal tissues, and what the relative levels of expression are. For example, the gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather than from a matched tissue sample (i.e., healthy lung and colon), while the literature shows that matched tissue samples are the standard (Pennica et al.; cited in the Office Action of 20 October 2004). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen; cited in the Office Action of 20 October 2004). Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1097 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (see *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689)).

Pooling 10 samples of blood for a control introduces variability in the assay. Utilization of incorrect tissue for comparison (with the absence of, or diminished expression of a gene in a particular tissue) would artificially increase or decrease the magnitude of differences observed in the instant assay. Likewise, using tumor and control samples from *different* subjects introduces variability into the gene amplification assay, making it less comparable and accurate.

One skilled in the art cannot determine if the "overexpression" of PRO1097 in Table 9B of the instant specification is statistically significant because of the lack of qualitative or numerical results. It is not clear what the "cutoff ratio" values are. There is no guidance in the specification as to the values above the "cutoff ratio" or how high the levels of overexpression are. If a clinician took a colon tissue sample from a patient with suspected colon cancer, what is the likelihood that when compared with normal tissue, the level of PRO1097 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Applicant has provided no indication of the nature or number of samples that were used. The only thing Applicants teach is that PRO1097 was "more highly expressed", and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. The specification also does not disclose at what stage of differentiation the lung and colon cancer samples were at or if the finding can be generalized to all lung and colon tumors. Relevant literature cautions researchers from drawing conclusions based on small changes in

transcript expression levels between normal and cancerous tissue (see for example, Hu et al. and Chen et al.). Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

The PRO1097 gene and polypeptides of the instant application have not been associated with tumor formation or the development of cancer, nor have they been shown to be predictive of such. The specification merely demonstrates that PRO1097 was purportedly overexpressed in three cancer samples. No mutation or translocation of PRO1097 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1097 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the PRO1097 gene is amplified in three samples and invites the artisan to determine the significance of this increase.

Applicants assert that the data of Example 170 clearly establishes the association between PRO1097 and tumor. They submit that it is sufficient to provide a single patentable utility, which has been done by showing that PRO1097 polypeptide is a diagnostic marker for lung and colon tumors. Applicant notes that there is no requirement that the specification provide a physiological or biochemical explanation regarding how the claimed polypeptide provides the useful function of being a diagnostic of lung and colon cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. 35 U.S.C. §101 does require a specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world" context of use which does not require significant further research. In the instant case, the specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed PRO1097 polypeptides. Without such information, how can one skilled in the art use the claimed invention in a meaningful manner? See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Regarding the second declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 5 July 2006, Applicants characterize the Declaration as setting forth Dr. Polakis' experience with gene amplification analysis. Applicants conclude that all of the submitted evidence supports the position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. The declaration of Dr. Polakis was previously considered by the Examiner in the Office Action of 20 October 2004. Applicant's arguments and the Polakis declaration have been fully considered but are not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v.

Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. There is no specific indication in the Polakis declaration that PRO1097 mRNA was elevated and correlated with increased protein levels. (2) It is important to note that the instant Specification only discloses gene amplification data for PRO1097 (i.e., data regarding amplification of PRO1097 genomic DNA), and does not disclose any information regarding PRO1097 mRNA or protein levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Hu et al., and Haynes et al., cited previously. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data are not included in the Declaration so that the examiner could independently evaluate them. For example, how highly amplified were the genes that correlated with increased polypeptide levels in Exhibit B?

The PRO1097 polynucleotide and polypeptide do not have a substantial utility because basic research is required to study the properties and activity of the polynucleotide that encodes the polypeptide of SEQ ID NO: 349. Until some actual and specific significance can be

attributed to the protein identified in the specification as PRO1097, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it.

In conclusion, it is noted that M.P.E.P. § 2107(I) states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO1097 polypeptides are useful as diagnostic markers for cancer or as therapeutic targets for cancer drugs is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO1097 polypeptide to be useful as a cancer diagnostic or therapeutic target, there must be a detectable change in the amount or form of PRO1097 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy tissue or cancerous tissue (see Haynes et al. and Hu et al.,.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO1097 polypeptides can be used as a cancer diagnostic agent.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments (5 July 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a credible, substantial, and asserted utility has been disclosed above for the polypeptide of PRO1097. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1097 polypeptide has a specific and substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the PRO1097 polypeptide.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at p. 9-11 of the previous Office Action (20 October 2004). Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 349 and still retain the function of SEQ ID NO: 349. Applicants

have not addressed the Written Description rejection, so the rejection remains as a matter of record.

Conclusion

No claims are allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
26 September 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER